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(54) Title: TREATMENT OF DISEASE STATES WHICH RESULT FROM NEOPLASTIC CELL PROLIFERATION USING PPAR-GAMMA ACTIVATORS AND COMPOSITIONS USEFUL THEREFOR

(57) Abstract

In accordance with the present invention, it has been discovered that PPARγ is expressed consistently in tissues associated with each of a variety of disease states which result from neoplastic cell proliferation. It has further been discovered that maximal activation of PPARγ with exogenous ligand promotes terminal differentiation of primary cells which are otherwise subject to neoplastic cell proliferation. In accordance with another aspect of the invention, it has been discovered that RXR-specific ligands are also potent agents for induction of differentiation of cells expressing the PPARγ/RXRα heterodimer, and that simultaneous treatment of cells subject to neoplastic cell proliferation with a PPARγ-selective ligand, in combination with an RXR-specific ligand, results in an additive stimulation of differentiation. Thus, the effect of neoplastic cell proliferation can be ameliorated by treatment of cells undergoing neoplastic cell proliferation with PPARγ agonists, optionally in the further presence of RXR agonists, thereby blocking further proliferation thereof. Accordingly, compounds and compositions which are useful for the treatment of a variety of disease states which result from neoplastic cell proliferation have been identified and are described herein.

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Treatment of Disease States Which Result from Neoplastic Cell Proliferation Using PPAR-Gamma Activators and Compositions Useful Therefor

FIELD OF THE INVENTION

The present invention relates to methods for the treatment of disease states which result from neoplastic cell proliferation. In another aspect, the present invention relates to compounds and compositions which are useful for carrying out the above-referenced methods.

BACKGROUND OF THE INVENTION

Neoplastic cell proliferation is the underlying cause of a wide variety of diseases, e.g., breast cancer, leukemia, colon cancer, prostate cancer, and the like. Traditional approaches to treatment of neoplastic cell proliferation include surgery, chemotherapy, radiotherapy, and the like, as well as combinations thereof. Unfortunately, conventional methods for the treatment of neoplastic cell proliferation require major invasive procedures, induce a variety of undesirable side effects, and/or lead to complete response in only a small percentage of cases. Thus, for many patients, conventional methods of treatment are largely palliative.

Induction of terminal differentiation represents a promising alternative to conventional methods of treatment for certain malignancies. For example, the retinoic acid receptor alpha (RARα), which plays an important role in the differentiation and malignant transformation of cells of myelocytic lineage, has been used as a target for intervention in acute promyelocytic leukemia. Indeed, differentiation therapy with all-trans retinoic acid has become the standard of care for this disease. In view of this success, it has been speculated

that nuclear receptors that regulate growth and differentiation of other cell types may also represent potential targets for differentiation therapy.

Accordingly, the development of effective, non-invasive methods for treating a variety of disease states which result from neoplastic cell proliferation would represent a significant advancement in the therapeutic arts.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention, we have discovered that PPARγ is expressed consistently in tissues associated with each of a variety of disease states which result from neoplastic cell proliferation. It has further been discovered that maximal activation of PPARγ with exogenous ligand promotes terminal differentiation of primary cells which are otherwise subject to neoplastic cell proliferation. Thus, cells undergoing neoplastic cell proliferation can be induced to differentiate, thereby blocking further proliferation thereof.

In accordance with the present invention, it has still further been discovered that RXR-specific ligands are also potent agents for induction of differentiation of cells expressing the PPARγ/RXRα heterodimer, and that simultaneous treatment of cells subject to neoplastic cell proliferation with a PPARγ-selective ligand, in combination with an RXR-specific ligand, results in an additive stimulation of differentiation. Accordingly, according to the invention, there have been identified compounds and compositions which are useful for the treatment of a variety of disease states which result from neoplastic cell proliferation.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 presents growth curves for the growth of HL-60 cells treated with various ligands for PPARγ and/or RXR. In the Figure, open circles represent the control (no ligand addition), darkened circles represent administration of 9-cis retinoic acid (9-cis RA), open boxes represent administration of LG268, darkened boxes represent administration of prostaglandin J2 and "X" represents co-administration of LG268 and PG-J2.

Figure 2 presents a cell cycle analysis of HL-60 cells when treated with various ligands for PPARγ and/or RXR. In the Figure, the darkened portion of each graph represents that proportion of the cell population in G1 phase, the white portion of each graph represents that proportion of the cell population in S phase, and the striped portion of each graph represents that proportion of the cell population in G2 phase.

DETAILED DESCRIPTION OF THE INVENTION

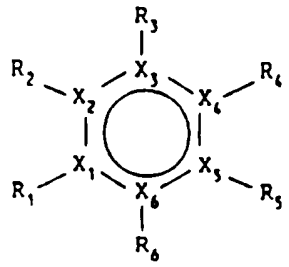
In accordance with the present invention, there are provided methods for the treatment of subjects suffering from disease states which are the result of neoplastic cell proliferation of cells which express PPAR-γ, said method comprising administering to said subject an amount of a therapeutic composition effective to ameliorate the effect of neoplastic cell proliferation on said cells, wherein said therapeutic composition comprises at least one PPAR-γ activator in a pharmaceutically acceptable carrier therefor. Optionally, therapeutic compositions employed in the practice of the present invention can also contain at least one retinoid X receptor (RXR) selective agonist. Invention methods can also be used in a prophylactic manner, i.e., to prevent the onset

of disease states which are the result of neoplastic cell proliferation of cells which express PPAR-γ.

A variety of disease states have been discovered to be the result of neoplastic cell proliferation of cells which express PPAR-γ, and thus are amenable to treatment (and/or prevention) according to the present invention. Such disease states include, for example, breast cancer, myelogenous leukemia, colon cancer, prostate cancer, liposarcomas, and the like.

A variety of PPAR-γ activators are suitable for use in the practice of the present invention. Thus, for example, aromatic compounds bearing at least one heteroatom-containing cyclic moiety (e.g., thiazolidinediones), PPARγ-selective prostaglandins, and the like, are contemplated for use in the practice of the present invention.

Exemplary PPARγ activators contemplated for use in the practice of the present invention include aromatic compounds bearing at least one heteroatom-containing cyclic moiety. Such compounds can be described broadly with reference to the general structure I:



(I)

wherein:

each of X_1, X_2, X_3, X_4, X_5 and X_6 is independently carbon, nitrogen, oxygen or sulfur, with the

proviso that at least three of the atoms forming the ring are carbon,

R_1 is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, alkenylaryl, substituted alkenylaryl, alkynylaryl, substituted alkynylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, poly(alkylene oxide), substituted poly(alkylene oxide), poly(alkylene sulfide), substituted poly(alkylene sulfide), poly(alkylene amine), substituted poly(alkylene amine), -OR, -SR or $-NR_2$, wherein each R is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, poly(alkylene oxide), substituted poly(alkylene oxide), poly(alkylene sulfide), substituted poly(alkylene sulfide), poly(alkylene amine) or substituted poly(alkylene amine); with R_1 having in the range of 2 up to 15 carbon atoms being preferred;

R_2 is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, alkenylaryl, substituted alkenylaryl, alkynylaryl, substituted alkynylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, oxyalkyl, poly(alkylene oxide) or

substituted poly(alkylene oxide); with R_2 having in the range of 1 up to about 15 carbon atoms being preferred;

R_3 is hydrogen, hydroxy, halogen, alkoxy, lower alkyl, substituted lower alkyl, alkenyl, substituted alkenyl, alkynyl or substituted alkynyl; with R_3 having in the range of 0 up to about 6 carbon atoms being preferred;

R_4 is hydrogen, formyl, acyl, lower alkyl or substituted lower alkyl; with R_4 having in the range of 0 up to about 4 carbon atoms being preferred;

R_5 is hydrogen, hydroxy, lower alkoxy, lower alkyl, substituted lower alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl or halogen; with R_5 having in the range of 0 up to about 6 carbon atoms being preferred; and

R_6 is hydrogen, hydroxy, lower alkoxy, lower alkyl, substituted lower alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl or halogen; with R_6 having in the range of 0 up to about 6 carbon atoms being preferred.

Those of skill in the art recognize that the core ring of structure I can be any one of a number of different aromatic or pseudo-aromatic structures, e.g., a benzene ring, a pyridine ring, a pyrazine, an oxazine, and the like.

As employed herein, "lower alkyl" refers to straight or branched chain alkyl groups having in the range of about 1 up to 4 carbon atoms; "alkyl" refers to straight or branched chain alkyl groups having in the range of about 1 up to 12 carbon atoms; "substituted alkyl" refers to alkyl groups further bearing one or more substituents such

as hydroxy, alkoxy (of a lower alkyl group), mercapto (of a lower alkyl group), halogen, trifluoromethyl, cyano, nitro, amino, carboxyl, carbamate, sulfonyl, sulfonamide, heteroatom-containing cyclic moieties, substituted heteroatom-containing cyclic moieties, and the like.

As employed herein, "alkenyl" refers to straight or branched chain hydrocarbyl groups having at least one carbon-carbon double bond, and having in the range of about 2 up to 12 carbon atoms and "substituted alkenyl" refers to alkenyl groups further bearing one or more substituents as set forth above.

As employed herein, "alkynyl" refers to straight or branched chain hydrocarbyl groups having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkynyl" refers to alkynyl groups further bearing one or more substituents as set forth above.

As employed herein, "aryl" refers to aromatic groups having in the range of 6 up to 14 carbon atoms and "substituted aryl" refers to aryl groups further bearing one or more substituents as set forth above.

As employed herein, "alkylaryl" refers to alkyl-substituted aryl groups and "substituted alkylaryl" refers to alkylaryl groups further bearing one or more substituents as set forth above.

As employed herein, "alkenylaryl" refers to alkenyl-substituted aryl groups and "substituted alkenylaryl" refers to alkenylaryl groups further bearing one or more substituents as set forth above.

As employed herein, "alkynylaryl" refers to alkynyl-substituted aryl groups and "substituted

alkynylaryl" refers to alkynylaryl groups further bearing one or more substituents as set forth above.

As employed herein, "arylalkyl" refers to aryl-substituted alkyl groups and "substituted arylalkyl" refers to arylalkyl groups further bearing one or more substituents as set forth above.

As employed herein, "arylalkenyl" refers to aryl-substituted alkenyl groups and "substituted arylalkenyl" refers to arylalkenyl groups further bearing one or more substituents as set forth above.

As employed herein, "arylalkynyl" refers to aryl-substituted alkynyl groups and "substituted arylalkynyl" refers to arylalkynyl groups further bearing one or more substituents as set forth above.

As employed herein, "poly(alkylene oxide)" refers to compounds having the general structure:

$$-[(CR'_2)_x-O]_y-H,$$

wherein each R' is independently hydrogen or lower alkyl, x falls in the range of 1 up to about 4 and y falls in the range of 2 up to about 8; "substituted poly(alkylene oxide)" refers to poly(alkylene oxide) groups further bearing one or more substituents as set forth above.

As employed herein, "poly(alkylene sulfide)" refers to compounds having the general structure:

$$-[(CR'_2)_x-S]_y-H,$$

wherein R', x and y are as defined above; "substituted poly(alkylene sulfide)" refers to poly(alkylene sulfide)

groups further bearing one or more substituents as set forth above.

As employed herein, "poly(alkylene amine)" refers to compounds having the general structure:

$$-[(CR'_2)_x-N(R')]_y-H,$$

wherein R', x and y are as defined above; "substituted poly(alkylene amine)" refers to poly(alkylene amine) groups further bearing one or more substituents as set forth above.

As employed herein, "acyl" refers to alkyl-carbonyl species.

As employed herein, "halogen" or "halo" refers to fluoro substituents, chloro substituents, bromo substituents or iodo substituents.

In a presently preferred aspect of the present invention, "R_1" of Formula I is selected from:

$$-Y_n-(CR"R")_m-Z,$$
$$-Y_n-(CR"R")_{m'}-O-(CR"R")_{m''}-Z, \text{ or}$$
$$-Y_n-(CR"R")_{m'''}-N(R''')-(CR"R")_{m''''}-Z,$$

wherein:

Y is -O- or -S-,

n is 0 or 1,

each R" is independently hydrogen, lower alkyl, substituted lower alkyl, hydroxy, lower alkoxy, thioalkyl, halogen, trifluoromethyl, cyano, nitro, amino, carboxyl, carbamate, sulfonyl or sulfonamide,

R''' is hydrogen, lower alkyl or substituted allkyl,

m falls in the range of 1 up to 15,

each m' falls independently in the range of 1 up to 8,

each m" falls independently in the range of 0 up to 12, and

Z is a heteroatom-containing cyclic moiety, a substituted heteroatom-containing cyclic moiety, cyano, nitro, amino, carbamate, $-OR^a$, wherein R^a is H, alkyl, alkenyl, alkynyl, acyl or aryl; $-C(O)R^b$, wherein R^b is H, alkyl, substituted alkyl, alkoxy, alkylamino, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, aryloxy, arylamino, alkylaryl, substituted alkylaryl, alkenylaryl, substituted alkenylaryl, alkynylaryl, substituted alkynylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic or trifluoromethyl; $-CO_2R^c$, wherein R^c is H, alkyl, alkenyl, alkynyl or aryl; $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$ or $-S(O)_2NHR^a$, wherein each R^a is as defined above, and the like.

As employed herein, "heteroatom-containing cyclic moiety" refers to cyclic (i.e., 5-, 6- or 7-membered ring-containing) groups containing one or more heteroatoms (e.g., N, O, S, or the like) as part of the ring structure, and having in the range of 1 up to about 14 carbon atoms; and "substituted heteroatom-containing cyclic moiety" refers to heterocyclic groups further bearing one or more substituents as set forth above. Examples of heteroatom-containing cyclic moieties include furans, thiophenes, pyrroles, pyrazoles, diazoles, triazoles, tetrazoles,

dithioles, oxathioles, oxazoles, isoxazoles, thiazoles, isothiazoles, oxadiazoles, oxatriazoles, dioxazoles, oxathiazoles, pyrans, pyrones, dioxins, pyridines, pyrimidines, pyrazines, pyridazines, piperazines, diazines, triazines, oxazines, isoxazines, oxathiazines, oxadiazines, morpholines, azepins, oxepins, thiopins, diazepins, benzothiazoles, thiazolidinediones, and the like.

Although the present invention is drawn broadly to the treatment of disease states associated with neoplastic cell proliferation, the treatment of liposarcomas is not contemplated by the above-described method of treatment when I is a thiazolidinedionyl moiety.

It is presently preferred that Z be selected from heteroatom-containing cyclic moieties, with polyheteroatom-containing cyclic moieties being especially preferred. Those of skill in the art can readily identify numerous groups which fall within the definition of "heteroatom-containing cyclic moieties", as set forth herein. Especially preferred are polyheteroatom-containing cyclic moieties, e.g., pyrazoles, diazoles, triazoles, tetrazoles, dithioles, oxathioles, oxazoles, isoxazoles, thiazoles, isothiazoles, oxadiazoles, oxatriazoles, dioxazoles, oxathiazoles, pyridazines, piperazines, diazines, triazines, oxazines, isoxazines, oxathiazines, oxadiazines, morpholines, diazepins, thiazolidinediones, and the like.

Especially preferred compounds employed in the practice of the present invention are those wherein "R_1" of Formula I is:

$$-Y_n-(CH_2)_x-Z$$

wherein:

Y is -O- or -S-,

n is 0 or 1,

x falls in the range of 2 up to 12; and
Z is a triazolyl moiety, a tetrazolyl moiety, an oxadiazolyl moiety, an oxatriazolyl moiety, a dioxazolyl moiety, an oxathiazolyl moiety, a triazinyl moiety, an isoxazinyl moiety, an oxathiazinyl moiety, an oxadiazinyl moiety, a thiazolidinedionyl moiety, and the like.

Presently preferred species of R_1 include $-O-(CH_2)_4-$[tetrazolinyl moieties] and $-O-(CH_2)_y-$thiazolidenedionyl moieties (wherein y falls in the range of about 2 up to 8).

In another preferred aspect of the present invention, "R_2" of Formula I is methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, butoxy, and the like.

In yet another preferred aspect of the present invention, "R_3" of Formula I is hydrogen, hydroxy, alkoxy, and the like.

In still another preferred aspect of the present invention, "R_4" of Formula I is formyl, acyl, a thiazolidenedionyl moiety, and the like.

In a further preferred aspect of the present invention, "R_5" of Formula I is hydrogen.

In a still further preferred aspect of the present invention, "R_6" of Formula I is hydrogen.

In yet another preferred aspect of the present invention, at least one of R_2, R_3, R_4, R_5 and R_6 (in addition to R_1) is not hydrogen. It is especially preferred that at least two of R_2, R_3, R_4, R_5 and R_6 (in addition to R_1) are not hydrogen. A plurality of substituents on the ring of structure I is especially preferred when x, m or the sum of

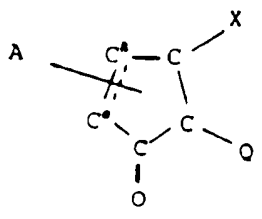
(m' + m"), with reference to the backbone of R_1, is less than or equal to 6.

Presently preferred species contemplated for use in the practice of the present invention include compounds wherein:

R_1 is $-O-(CH_2)_4-$[tetrazolinyl moiety] or $-O-(CH_2)_y-$thiazolidenedionyl moiety, wherein y falls in the range of about 2 up to 8,
R_2 is hydrogen or lower alkyl,
R_3 is hydroxy or alkoxy,
R_4 is acyl or a thiazolidenedionyl moiety; and
R_5 and R_6 are each hydrogen.

The above-described compounds can be readily prepared using a variety of synthetic methods, as are well known by those of skill in the art. For example, many of the above-described compounds can be prepared chemically or enzymatically.

Exemplary PPARγ activators contemplated for use in the practice of the present invention also include PPAR-γ-selective prostaglandins or prostaglandin-like compounds. Such prostaglandins include members of the prostaglandin-J_2 family of compounds (e.g., prostaglandin-J_2, Δ^{12}-prostaglandin-J_2 or 15-deoxy-$\Delta^{12,14}$-prostaglandin-J_2), members of the prostaglandin-D_2 family of compounds (e.g., prostaglandin-D_2), or precursors thereof, as well as compounds having the structure II:



(II)

wherein:

A is selected from hydrogen or a leaving group at the α- or ß- position of the ring, or A is absent when there is a double bond between C^a and C^b of the ring;

X is an alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl or substituted alkynyl group having in the range of 2 up to 15 carbon atoms; and

Q is an alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl or substituted alkynyl group having in the range of 2 up to 15 carbon atoms.

As employed herein, the term "leaving group" refers to functional groups which can readily be removed from the precursor compound, for example, by nucleophilic displacement, under E_2 elimination conditions, and the like. Examples include hydroxy groups, alkoxy groups, tosylates, brosylates, halogens, and the like.

As employed herein, "cycloalkyl" refers to cyclic ring-containing groups containing in the range of about 3 up to 8 carbon atoms, and "substituted cycloalkyl" refers to cycloalkyl groups further bearing one or more substituents as set forth above.

As employed herein, "heterocyclic" refers to cyclic (i.e., ring-containing) groups containing one or more heteroatoms (e.g., N, O, S, or the like) as part of the ring structure, and having in the range of 3 up to 14 carbon atoms and "substituted heterocyclic" refers to heterocyclic groups further bearing one or more substituents as set forth above.

In a presently preferred aspect of the present invention, "X" of Formula II is selected from:

$-(CRR)_m-Z'$,

$-(CRR)_{m'}-C(R)=C(R)-(CRR)_{m'}-Z'$, or

$-(CRR)_{m''}-C\equiv C-(CRR)_{m''}-Z'$, wherein:

each R is independently H, lower alkyl, substituted lower alkyl, hydroxy, lower alkoxy, thioalkyl, halogen, trifluoromethyl, cyano, nitro, amino, carboxyl, carbamate, sulfonyl or sulfonamide,

m falls in the range of 1 up to 15,

each m' falls independently in the range of 0 up to 12, with the proviso that the total chain length of the alkenyl moiety does not exceed 15 carbon atoms,

each m" falls independently in the range of 0 up to 12, with the proviso that the total chain length of the alkynyl moiety does not exceed 15 carbon atoms, and

Z' is a polar, heteroatom-containing substituent.

Those of skill in the art can readily identify numerous groups which satisfy the requirement that Z' be a polar, heteroatom-containing (i.e., O, N, S, or the like) substituent. Thus, Z' can be selected from cyano, nitro, amino, carbamate, or a substituent having the structure:

$-CH_2OR'$, wherein R' is H, alkyl, alkenyl, alkynyl, acyl, aryl, or the like;

-C(O)R", wherein R" is H, alkyl, substituted alkyl, alkoxy, alkylamino, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, aryloxy, arylamino, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, heterocyclic, substituted heterocyclic or trifluoromethyl,

$-CO_2R'''$, wherein R''' is selected from H, alkyl, alkenyl, alkynyl, or the like;

$-SR'$, $-S(O)R'$, $-S(O)_2R'$ or $-S(O)_2NHR'$, wherein each R' is as defined above,

and the like.

Especially preferred compounds employed in the practice of the present invention are those wherein "X" of Formula II is:

$-CRR-C(R)=C(R)-(CRR)_m-Z'$, wherein:

each R is independently selected from H, lower alkyl, substituted lower alkyl, hydroxy, alkoxy (of a lower alkyl group), halogen, trifluoromethyl, amino, carboxyl or sulfonyl,

m falls in the range of 1 up to 6, and

Z' is selected from $-CH_2OH$, $-CH_2OAc$, $-CO_2H$, $-CO_2Me$ or $-CO_2Et$.

In another preferred aspect of the present invention, "Q" of Formula II is selected from:

$=C(R)-[C(R)=C(R)]_n-(CRR)_{n'}-Z''$ (III),

$=C(R)-[C\equiv C]_{n''}-(CRR)_{n'}-Z''$ (IIIA),

$=C(R)-CRR-CR(R')-(CRR)_{n'}-Z''$ (IV),

$-[C(R)=C(R)]_n-(CRR)_{n'}-Z''$ (V), or

$-[C\equiv C]_n-(CRR)_{n'}-Z''$ (VA),

wherein

each R is independently as defined above,

each R' is independently H, lower alkyl, substituted lower alkyl or a leaving group,

Z'' is H, lower alkyl or substituted lower alkyl,

n falls in the range of 0 up to 4,

n' falls in the range of 2 up to 12, and

n'' falls in the range of 1 up to 3.

Especially preferred compounds contemplated for use in the practice of the present invention include those wherein "Q" of Formula II is selected from:

=C(R)-C(R)=C(R)-$(CRR)_{n'}$-Z" (III),

=C(R)-CRR-CR(R')-$(CRR)_{n'}$-Z" (IV), or

-C(R)=C(R)-CR(R')-$(CRR)_{n'}$-Z" (V), wherein

each R and each R' is independently as defined above,

Z" is H, lower alkyl or substituted lower alkyl, and

n' falls in the range of 1 up to 6.

Presently most preferred compounds for use in the practice of the present invention include those wherein "Q" of Formula II is:

=C(R)-C(R)=C(R)-$(CRR)_{n'}$-Z" (III), wherein

each R is H, lower alkyl or substituted lower alkyl,

n is 1,

n' falls in the range of about 2 up to 6, and

Z" is H or lower alkyl;

or compounds wherein "Q" of Formula II is:

=C(R)-CRR-CR(R')-$(CRR)_{n'}$-Z" (IV) or

-C(R)=C(R)-CR(R')-$(CRR)_{n'}$-Z" (V), wherein

each R is H, lower alkyl or substituted lower alkyl,

R' is H, lower alkyl, or an hydroxy group,

n is 1,

n' falls in the range of about 2 up to 6, and

Z" is H or lower alkyl.

Referring to the structural formulae set forth above, prostaglandin-D_2 (Pg-D2) is described by Formula II

(as set forth above), wherein A is 9-OH, Q is V, each R is hydrogen, R' is hydroxy, Z' is $-CO_2H$, m is 3, Z" is methyl, n is 1 and n' is 4; prostaglandin-J_2 (Pg-J2) is described by Formula II, wherein A is absent, Q is V, each R is hydrogen, R' is hydroxy, Z' is $-CO_2H$, m is 3, Z" is methyl, n is 1 and n' is 4; Δ^{12}-prostaglandin-J_2 (Δ^{12}-Pg-J2) is described by Formula II, wherein A is absent, Q is IV, each R is hydrogen, R' is hydroxy, Z' is $-CO_2H$, m is 3, Z" is methyl, n is 1 and n' is 4; 15-deoxy-$\Delta^{12,14}$-prostaglandin-J_2 (15-deoxy-$\Delta^{12,14}$-Pg-J2) is described by Formula II, wherein A is absent, Q is II, each R is hydrogen, Z' is $-CO_2H$, m is 3, Z" is methyl, n is 1 and n' is 4.

The above-described compounds can be readily prepared using a variety of synthetic methods, as are well known by those of skill in the art. For example, many of the above-described compounds can be prepared chemically or enzymatically, from the naturally occurring precursor, arachidonic acid.

RXR selective ligands contemplated for use in the practice of the present invention include substituted benzoic acids or derivatives thereof (e.g., substituted benzoates), substituted nicotinic acids or derivatives thereof (e.g., substituted nicotinates), substituted carboxylated furans, and the like. Exemplary agonists contemplated for use herein include 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]benzoic acid, 1,3-propylene glycol ketal of 4-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]benzoic acid, methyl 4-[(3,8,8-trimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]benzoate, methyl 4-[(3,5,5-trimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]benzoate, methyl 4-[(1,1,2,3,3,6-hexamethylindan-5-yl)carbonyl]benzoate, methyl 6-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]nicotinate, methyl 4-[1-(3,8,8-trimethyl-

5,6,7,8-tetrahydro-2-naphthalen-2-yl)ethenyl]benzoate, methyl 4-[1-(3,5,5-trimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethenyl]benzoate, methyl 4-[1-(1,1,2,3,3,6-hexamethylindan-5-yl)ethenyl]benzoate, methyl 6-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethenyl]nicotinate, 4-[1-(3,8,8-trimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethenyl]benzoic acid, 4-[1-(3,5,5-trimethyl-5,6,7,8-tetrahydro-2-naphthalen-2-yl)ethenyl]benzoic acid, 4-[1-(1,1,2,3,3,6-hexamethylindan-5-yl)ethenyl]benzoic acid, 6-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethenyl]nicotinic acid, methyl 4-[1-methyl-1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]benzoate, 4-[2-methyl-1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]benzoic acid, 4-[1-methyl-1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]benzoic acid, 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]benzoic acid, methyl 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]benzoate, methyl 4-[2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxiranyl]benzoate, methyl 6-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]nicotinate, 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]benzoic acid, 4-[2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxiranyl]benzoic acid, 6-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]nicotinic acid (also referred to in the art as "LG268"), 3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-ol, methyl 4-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)methyl]benzoate, methyl 4-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]benzoate, 4-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)methyl]benzoic acid, 4-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]benzoic acid, methyl 2-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-

yl)carbonyl]benzoate, methyl 3-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]benzoate, 2-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]benzoic acid, 3-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]benzoic acid, the carboxylated furan derivative referred to as AGN191701 (see Mol. and Cell. Biol. 15:3540-3551 (1995)), and the like.

Presently preferred RXR selective agonists contemplated for use herein include 6-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]nicotinic acid (LG268) and 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethenyl]benzoic acid.

In accordance with another embodiment of the present invention, there are provided methods for modulating growth of neoplastic cells, wherein said growth is mediated by peroxisome proliferator activated receptor-gamma (PPAR-γ), said method comprising contacting said cells with a composition effective to modulate said growth, wherein said composition comprises at least one PPAR-γ activator in a pharmaceutically acceptable carrier therefor.

As employed herein, the term "modulate" refers to the ability of a modulator for PPARγ to either directly (by binding to the receptor as a ligand) or indirectly (as a precursor for a ligand or an inducer which promotes production of ligand from a precursor) induce expression of gene(s) maintained under hormone expression control, or to repress expression of gene(s) maintained under such control.

As employed herein, the phrase "processes mediated by PPARγ" refers to biological, physiological,

endocrinological, and other bodily processes which are mediated by receptor or receptor combinations which are responsive to the PPAR-γ agonists described herein (e.g., cell differentiation to produce lipid-accumulating cells, to induce cell differentiation in a variety of other cell types, and the like). Modulation of such processes can be accomplished in vitro or in vivo. In vivo modulation can be carried out in a wide range of mammalian subjects, such as, for example, humans, rodents, sheep, pigs, cows, and the like.

As employed herein, the phrase "amount... effective to modulate..." refers to levels of compound (or composition) sufficient to provide circulating concentrations high enough to accomplish the desired effect. Such a concentration typically falls in the range of about 10 nM up to 2 μM; with concentrations in the range of about 100 nM up to 500 nM being preferred. As noted previously, since the activity of different compounds which fall within the definition of structures I and II as set forth above may vary considerably, and since individual subjects may present a wide variation in severity of symptoms, it is up to the practitioner to determine a subject's response to treatment and vary the dosages accordingly.

PPAR-γ-selective agonists (optionally in combination with RXR selective agonists) contemplated for use in the practice of the present invention can be employed for both in vitro and in vivo applications. For in vivo applications, the above-described compounds can be incorporated into a pharmaceutically acceptable formulation for administration. Those of skill in the art can readily determine suitable dosage levels when compounds contemplated for use in the practice of the present invention are so used.

In accordance with another embodiment of the present invention, there are provided compositions comprising at least one PPAR-γ-selective activator (as described herein), and at least one retinoid X receptor (RXR) selective agonist, optionally in a pharmaceutically acceptable carrier. Exemplary pharmaceutically acceptable carriers include carriers suitable for oral, intravenous, subcutaneous, intramuscular, intracutaneous, and the like administration. Administration in the form of creams, lotions, tablets, dispersible powders, granules, syrups, elixirs, sterile aqueous or non-aqueous solutions, suspensions or emulsions, and the like, is contemplated.

For the preparation of oral liquids, suitable carriers include emulsions, solutions, suspensions, syrups, and the like, optionally containing additives such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents, and the like.

For the preparation of fluids for parenteral administration, suitable carriers include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized, for example, by filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile water, or some other sterile injectable medium immediately before use.

The invention will now be described in greater detail by reference to the following non-limiting examples.

Example 1
Growth of HL-60 Cells in the Presence of Various Ligands

HL-60 cells were plated at a density of $2x10^5$ cells/ml and were treated with:

100 nM 9-cis retinoic acid (9-cis RA; which is both RAR and RXR active),

100 nM LG268 (which is RXR selective),

3 μM prostaglandin J2 (PG-J2; which is PPARγ active), or

a combination of 100 nM of LG268 and 3 μM of PG-J2.

Cell numbers were determined after 3, 5 or 7 days of culture, as illustrated in Figure 1.

The results show that 9-cis RA alone, and PG-J2 alone each inhibit cell growth, while LG268 alone has only a marginal ability to promote cell differentiation. The combination of PG-J2 and LG268, however, shows an enhanced ability to inhibit cell growth.

Example 2
Cell Cycle Analysis of HL-60 Cells When Grown in the Presence of Various Ligands

HL-60 cells were plated at a density of $2x10^5$ cells/ml and were treated with:

100 nM 9-cis retinoic acid (9-cis RA; which is both RAR and RXR active),

100 nM LG268 (which is RXR selective),

3 μM prostaglandin J2 (PG-J2; which is PPARγ active), or

a combination of 100 nM of LG268 and 3 μM of PG-J2.

Cell cycle analysis was carried out on day 3 using standard DNA content determination by flow cytometry. Results are presented graphically in Figure 2, and summarized in Table 1.

Table 1

	Cell Cycle Phase, %		
Sample	G1	S	G2
Control	58.7	30.1	11.2
9-cis RA	70.5	19.2	10.2
LG268	54.5	31.1	14.4
PG-J2	65.9	22.6	11.5
LG268 + PG-J2	76.9	15.1	8.0

The results show that treatment with either 9-cis RA (i.e., induction of the RARα pathway) or PG-J2 (i.e., induction of the PPARγ pathway) inhibits cell cycle progression and leads to the accumulation of cells in G1. Treatment of HL-60 cells with the combination of LG268 and PG-J2 produces a synergistic effect, whereby an increased number of cells accumulate in G1.

Example 3
Synergistic Induction of Differentiation in HL-60 and THP-1 Leukemia Cells When Treated With Ligands for PPARγ and RXRα

HL-60 and THP-1 leukemia cells were seeded at a density of $2x10^5$ cells/ml and cultured in RPMI containing 10% charcoal-stripped fetal calf serum. Cells were treated

with either vehicle alone, or 10 nM AM580, 100 nM LG268, or 3 μM 15-deoxy-Δ 12,14-prostaglandin-J2. After 5 days, cells were incubated with monoclonal antibody to the monocyte-specific differentiation antigen CD14, and analyzed by flow cytometry using a Becton Dickinson FACScan. Median fluorescence values for each culture are presented in Table 2.

Table 2

Sample	median fluorescence
A. HL-60 cells	
control	24
AM580	26
LG268	138
PG-J2	47
LG268/PG-J2	274
B. THP-1 cells	
control	13
LG268	18
PG-J2	16
LG268/PG-J2	58

Inspection of the data presented in Table 2 reveals that the combination of a PPARγ agonist (e.g., PG-J2) and an RXR agonist (e.g., LG268) dramatically increases the proportion of HL-60 and THP-1 cells which respond to a differentiation marker.

While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

That which is claimed is:

1. A method for treating a subject suffering from a disease state which is the result of neoplastic cell proliferation of cells which express PPAR-γ, said method comprising administering to said subject an amount of a therapeutic composition effective to ameliorate the effect of neoplastic cell proliferation on said cells, wherein said therapeutic composition comprises at least one PPAR-γ activator in a pharmaceutically acceptable carrier therefor.

2. A method according to claim 1 wherein said cells which express PPAR-γ are cancerous breast cells.

3. A method according to claim 1 wherein said cells which express PPAR-γ are myelogenous leukemia cells.

4. A method according to claim 1 wherein said cells which express PPAR-γ are cancerous colon cells.

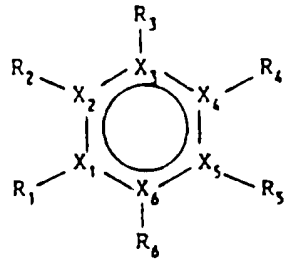
5. A method according to claim 1 wherein said cells which express PPAR-γ are cancerous prostate cells.

6. A method according to claim 1 wherein said PPAR-γ activator is a PPAR-γ-selective prostaglandin or prostaglandin-like compound or precursor thereof.

7. A method according to claim 6 wherein said PPAR-γ-selective prostaglandin is a prostaglandin-J_2, a prostaglandin-D_2, or a precursor thereof.

8. A method according to claim 7 wherein said prostaglandin-J_2 is prostaglandin-J_2, Δ^{12}-prostaglandin-J_2 or 15-deoxy-$\Delta^{12,14}$-prostaglandin-J_2.

9. A method according to claim 1 wherein said PPAR-γ activator has the structure I, wherein structure I is as follows:



(I)

wherein:

each of X_1, X_2, X_3, X_4, X_5 and X_6 is independently carbon, nitrogen, oxygen or sulfur, with the proviso that at least three of the atoms forming the ring are carbon,

R_1 is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, alkenylaryl, substituted alkenylaryl, alkynylaryl, substituted alkynylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, poly(alkylene oxide), substituted poly(alkylene oxide), poly(alkylene sulfide), substituted poly(alkylene sulfide), poly(alkylene amine), substituted poly(alkylene amine), -OR, -SR or $-NR_2$, wherein each R is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, poly(alkylene oxide), substituted poly(alkylene oxide),

poly(alkylene sulfide), substituted poly(alkylene sulfide), poly(alkylene amine) or substituted poly(alkylene amine);

R_2 is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, alkenylaryl, substituted alkenylaryl, alkynylaryl, substituted alkynylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, oxyalkyl, poly(alkylene oxide) or substituted poly(alkylene oxide);

R_3 is hydrogen, hydroxy, halogen, alkoxy, lower alkyl, substituted lower alkyl, alkenyl, substituted alkenyl, alkynyl or substituted alkynyl;

R_4 is hydrogen, formyl, acyl, lower alkyl or substituted lower alkyl;

R_5 is hydrogen, hydroxy, lower alkoxy, lower alkyl, substituted lower alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl or halogen; and

R_6 is hydrogen, hydroxy, lower alkoxy, lower alkyl, substituted lower alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl or halogen.

10. A method according to claim 9 wherein "R_1" of Formula I is:

$$-Y_n-(CR''R'')_m-Z,$$
$$-Y_n-(CR''R'')_{m'}-O-(CR''R'')_{m''}-Z, \text{ or}$$
$$-Y_n-(CR''R'')_{m'''}-N(R''')-(CR''R'')_{m''''}-Z,$$

wherein:

Y is -O- or -S-,

n is 0 or 1,

each R" is independently hydrogen, lower alkyl, substituted lower alkyl, hydroxy, lower alkoxy, thioalkyl, halogen, trifluoromethyl, cyano, nitro, amino, carboxyl, carbamate, sulfonyl or sulfonamide,

R''' is hydrogen, lower alkyl or substituted allkyl,

m falls in the range of 1 up to 15,

each m' falls independently in the range of 1 up to 8,

each m" falls independently in the range of 0 up to 12, and

Z is a heteroatom-containing cyclic moiety, a substituted heteroatom-containing cyclic moiety, cyano, nitro, amino, carbamate, $-OR^a$, wherein R^a is H, alkyl, alkenyl, alkynyl, acyl or aryl; $-C(O)R^b$, wherein R^b is H, alkyl, substituted alkyl, alkoxy, alkylamino, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, aryloxy, arylamino, alkylaryl, substituted alkylaryl, alkenylaryl, substituted alkenylaryl, alkynylaryl, substituted alkynylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic or trifluoromethyl; $-CO_2R^c$, wherein R^c is H, alkyl, alkenyl, alkynyl or aryl; $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$ or $-S(O)_2NHR^a$, wherein each R^a is as defined above.

11. A method according to claim 10 wherein Z is a polyheteroatom-containing cyclic moiety or a substituted polyheteroatom-containing cyclic moiety.

12. A method according to claim 10 wherein Z is a furan, thiophene, pyrrole, pyrazole, diazole, triazole, tetrazole, dithiole, oxathiole, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, oxatriazole, dioxazole, oxathiazole, pyran, pyrone, dioxin, pyridine, pyrimidine, pyrazine, pyridazine, piperazine, diazine, triazine, oxazine, isoxazine, oxathiazine, oxadiazine, morpholino, azepin, oxepin, thiopin, diazepin, benzothiazole or a thiazolidinedione.

13. A method according to claim 10 wherein Z is a pyrazole, diazole, triazole, tetrazole, dithiole, oxathiole, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, oxatriazole, dioxazole, oxathiazole, pyridazine, piperazine, diazine, triazine, oxazine, isoxazine, oxathiazine, oxadiazine, morpholine, diazepin or a thiazolidinedione.

14. A method according to claim 9 wherein "R_1" of Formula I is:

$$-Y_n-(CH_2)_x-Z$$

wherein:

Y is -O- or -S-,
n is 0 or 1,
x falls in the range of 2 up to 12; and
Z is a triazolyl moiety, a tetrazolyl moiety, an oxadiazolyl moiety, an oxatriazolyl moiety, a dioxazolyl moiety, an oxathiazolyl moiety, a triazinyl moiety, an isoxazinyl moiety, an oxathiazinyl moiety, an oxadiazinyl moiety, or a thiazolidinedionyl moiety.

15. A method according to claim 1 wherein said therapeutic composition further comprises at least one retinoid X receptor (RXR) selective agonist.

16. A method according to claim 15 wherein said retinoid X receptor (RXR) selective agonist is a substituted benzoic acid or derivative thereof, a substituted nicotinic acid or derivative thereofor or a substituted carboxylated furan.

17. A method according to claim 15 wherein said retinoid X receptor (RXR) selective agonist is 6-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]nicotinic acid (LG268).

18. A method according to claim 15 wherein said retinoid X receptor (RXR) selective agonist is 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethenyl]benzoic acid.

19. A method for modulating growth of neoplastic cells, wherein said growth is mediated by peroxisome proliferator activated receptor-gamma (PPAR-γ), said method comprising contacting said cells with a composition effective to modulate said growth, wherein said composition comprises at least one PPAR-γ activator in a pharmaceutically acceptable carrier therefor.

20. A method according to claim 19 wherein said composition further comprises at least one retinoid X receptor (RXR) selective agonist.

21. A method according to claim 20 wherein said retinoid X receptor (RXR) selective agonist is a substituted benzoic acid or derivative thereof, a substituted nicotinic acid or derivative thereof or a substituted carboxylated furan.

22. A method according to claim 20 wherein said retinoid X receptor (RXR) selective agonist is 6-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]nicotinic acid (LG268).

23. A method according to claim 20 wherein said retinoid X receptor (RXR) selective agonist is 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethenyl]benzoic acid.

24. A method according to claim 19 wherein said neoplastic cells are cancerous breast cells, myelogenous leukemia cells, cancerous colon cells or cancerous prostate cells.

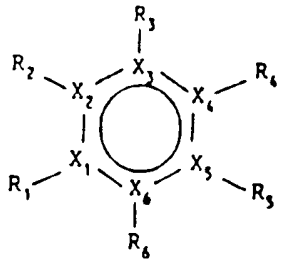
25. A composition comprising at least one PPAR-γ-selective activator and at least one retinoid X receptor (RXR) selective agonist.

26. A composition according to claim 25 wherein said PPAR-γ-selective activator is a prostaglandin or prostaglandin-like compound, or precursor thereof.

27. A composition according to claim 26 wherein said PPAR-γ-selective activator is a prostaglandin-J_2, a prostaglandin-D_2, or a precursor thereof.

28. A composition according to claim 27 wherein said prostaglandin-J_2 is prostaglandin-J_2, Δ^{12}-prostaglandin-J_2 or 15-deoxy-$\Delta^{12,14}$-prostaglandin-J_2.

29. A composition according to claim 25 wherein said PPAR-γ activator has the structure I, wherein structure I is as follows:



(I)

wherein:

each of X_1, X_2, X_3, X_4, X_5 and X_6 is independently carbon, nitrogen, oxygen or sulfur, with the proviso that at least three of the atoms forming the ring are carbon,

R_1 is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, alkenylaryl, substituted alkenylaryl, alkynylaryl, substituted alkynylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, poly(alkylene oxide), substituted poly(alkylene oxide), poly(alkylene sulfide), substituted poly(alkylene sulfide), poly(alkylene amine), substituted poly(alkylene amine), -OR, -SR or $-NR_2$, wherein each R is independently alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, poly(alkylene oxide), substituted poly(alkylene oxide), poly(alkylene sulfide), substituted poly(alkylene sulfide), poly(alkylene amine) or substituted poly(alkylene amine);

R_2 is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, alkenylaryl, substituted alkenylaryl, alkynylaryl, substituted alkynylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, oxyalkyl, poly(alkylene oxide) or substituted poly(alkylene oxide);

R_3 is hydrogen, hydroxy, halogen, alkoxy, lower alkyl, substituted lower alkyl, alkenyl, substituted alkenyl, alkynyl or substituted alkynyl;

R_4 is hydrogen, formyl, acyl, lower alkyl or substituted lower alkyl;

R_5 is hydrogen, hydroxy, lower alkoxy, lower alkyl, substituted lower alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl or halogen; and

R_6 is hydrogen, hydroxy, lower alkoxy, lower alkyl, substituted lower alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl or halogen.

30. A composition according to claim 29 wherein "R_1" of Formula I is:

$-Y_n-(CR"R")_m-Z$,

$-Y_n-(CR"R")_{m'}-O-(CR"R")_{m''}-Z$, or

$-Y_n-(CR"R")_{m'''}-N(R''')-(CR"R")_{m''''}-Z$,

wherein:

Y is -O- or -S-,

n is 0 or 1,

each R" is independently hydrogen, lower alkyl, substituted lower alkyl, hydroxy, lower alkoxy, thioalkyl,

halogen, trifluoromethyl, cyano, nitro, amino, carboxyl, carbamate, sulfonyl or sulfonamide,

R''' is hydrogen, lower alkyl or substituted allkyl,

m falls in the range of 1 up to 15,

each m' falls independently in the range of 1 up to 8,

each m" falls independently in the range of 0 up to 12, and

Z is a heteroatom-containing cyclic moiety, a substituted heteroatom-containing cyclic moiety, cyano, nitro, amino, carbamate, $-OR^a$, wherein R^a is H, alkyl, alkenyl, alkynyl, acyl or aryl; $-C(O)R^b$, wherein R^b is H, alkyl, substituted alkyl, alkoxy, alkylamino, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, aryloxy, arylamino, alkylaryl, substituted alkylaryl, alkenylaryl, substituted alkenylaryl, alkynylaryl, substituted alkynylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic or trifluoromethyl; $-CO_2R^c$, wherein R^c is H, alkyl, alkenyl, alkynyl or aryl; $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$ or $-S(O)_2NHR^a$, wherein each R^a is as defined above.

31. A composition according to claim 30 wherein Z is a polyheteroatom-containing cyclic moiety or a substituted polyheteroatom-containing cyclic moiety.

32. A composition according to claim 30 wherein Z is a furan, thiophene, pyrrole, pyrazole, diazole, triazole, tetrazole, dithiole, oxathiole, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, oxatriazole, dioxazole, oxathiazole, pyran, pyrone, dioxin, pyridine, pyrimidine, pyrazine, pyridazine, piperazine, diazine, triazine, oxazine, isoxazine, oxathiazine, oxadiazine, morpholino, azepin, oxepin, thiopin, diazepin, benzothiazole or a thiazolidinedione.

33. A composition according to claim 30 wherein Z is a pyrazole, diazole, triazole, tetrazole, dithiole, oxathiole, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, oxatriazole, dioxazole, oxathiazole, pyridazine, piperazine, diazine, triazine, oxazine, isoxazine, oxathiazine, oxadiazine, morpholine, diazepin or a thiazolidinedione.

34. A composition according to claim 29 wherein "R_1" of Formula I is:

$$-Y_n-(CH_2)_x-Z$$

wherein:

Y is -O- or -S-,
n is 0 or 1,
x falls in the range of 2 up to 12; and
Z is a triazolyl moiety, a tetrazolyl moiety, an oxadiazolyl moiety, an oxatriazolyl moiety, a dioxazolyl moiety, an oxathiazolyl moiety, a triazinyl moiety, an isoxazinyl moiety, an oxathiazinyl moiety, an oxadiazinyl moiety, or a thiazolidinedionyl moiety.

35. A composition according to claim 25 wherein said retinoid X receptor (RXR) selective agonist is a substituted benzoic acid or derivative thereof, a substituted nicotinic acid or derivative thereof or a substituted carboxylated furan.

36. A composition according to claim 35 wherein said retinoid X receptor (RXR) selective agonist is 6-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]nicotinic acid (LG268).

37. A composition according to claim 35 wherein said retinoid X receptor (RXR) selective agonist is 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethenyl]benzoic acid.

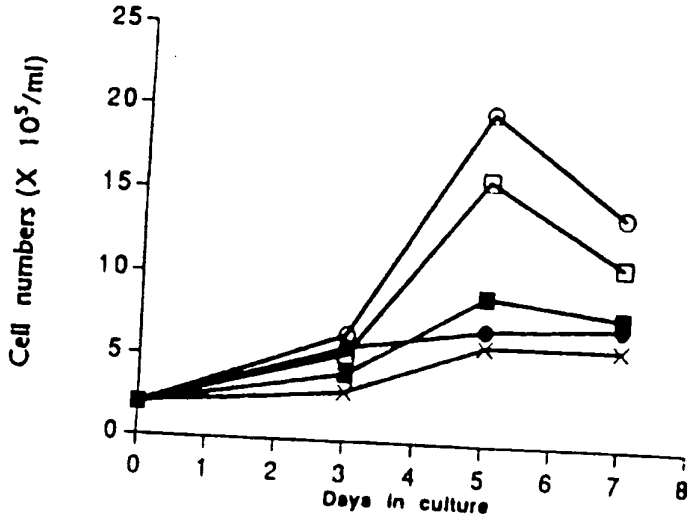
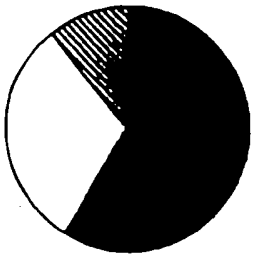
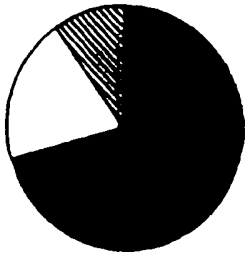


Figure 1

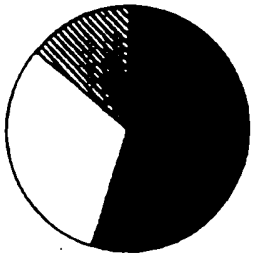
Cell cycle analysis of HL-60 cells (day3)



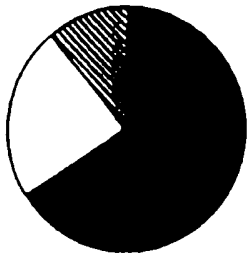
control



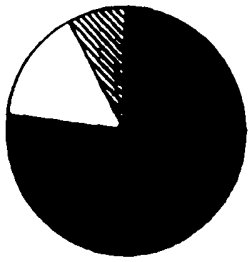
9-cisRA



LG268



PG-J2



LG268 + PG-J2

Figure 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/24190

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/20, 31/44, 31/38, 31/19
US CL :514/559, 342, 448, 569
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/559, 342, 448, 569

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,399,586 A (DAVIES et al.) 21 March 1995, the abstract and column 10.	15-18, 20-23, 25-37
Y — X	Database EMBASE on STN, Elsevier Science B.V. , AN 91178677, SASAKI, H. et al. 'Human ovarian cancer cell lines resistant to cisplatin, doxorubicin, and L-phenylalanine mustard are sensitive to .DELTA.7-prostaglandin A1 and .DELTA.12- prostaglandin J2' abstract, Gynecol. Oncol., 1991 41/1 (36-40).	1-8, 15-18, 20-28, 35-37 ——— 19
Y — X	Database EMBASE on STN, Elsevier Science B.V., AN 91162472, CONDE, B. et al. 'Modulation of cell growth and differentiation induced by prostaglandin D2 in the glioma cell line C6' abstract, Anticancer Res., 1991, 11/1 (289-295).	1-8, 15-18, 20-28, 35-37 ——— 19

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 MARCH 1998	10 APR 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer M. MOEZIE Telephone No. (703) 308-1235

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/24190

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,561,147 A (TAKATANI et al.) 01 October 1996, column 23, lines 55-65 and columns 97-116.	1-5, 9-25, 29-37
Y	Database MEDLINE on STN, US National Library of Medicine, (Bethesda, MD, USA), No. 96313832, SCHOONJANS, K. et al. 'The peroxisome proliferator activated receptors (PPARS) and their effects on lipid metabolism and adipocyte differentiation' abstract, Biochimica Et Biopyhsica Acta (NL), 26 July 1996 1302 (2) 93-109.	25-37

Form PCT/ISA/210 (continuation of second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/24190

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

USPATFULL, MEDLINE, HCAPLUS- compounds herein for the treatment of cancerous conditions and for the treatment of conditions of neoplastic cell proliferation of cells expressing PPAR gamma employing PPAR gamma activators and RXR agonists.

Form PCT/ISA/210 (extra sheet)(July 1992)*